II

THE CONQUEST OF MALARIA*

I AM going to consider with you this afternoon the Conquest of Malaria, not as an accomplished fact, for it is far from that, but as a possibility in the not-too-far-distant future, at least in our own country.

It may be surprising to some of you who may never have seen a case of malaria to learn that malaria is the most important human disease in the world today, surpassing any others not only in the amount of sickness it causes and economic loss it entails, but also in the number of deaths for which it is responsible. It is a stubborn disease, usually slow to kill, quick to incapacitate, and hard to cure. It is a disease that cannot be controlled by individual effort, but requires community effort, sometimes even international coöperation, as was demonstrated in the threat to all the Americas by the outbreak in Brazil less than a decade ago, brought on by the accidental introduction by airplane of a particularly dangerous vector from Africa.

Its ravages in some parts of the world are almost unbelievable. In India alone there are something like 100,000,000 cases annually, and from 1,000,000 to 2,000,000 deaths. In some places in Africa nine out of every ten infants die before they are a year old, due to a very large extent, directly or indirectly, to malaria. Malaria has held back the development of the tropics for centuries, and has been an important con-

*A public lecture delivered on November 24, 1946, by Asa C. Chandler, Ph. D., Professor of Biology of the Rice Institute.

tributing cause to the downfall of empires and to the deplorably low economic condition of some potentially prosperous countries.

This disease, under other names, was recognized as a human scourge for centuries before the birth of Christ. The ancient Greeks and Romans were familiar with it, and did not fail to associate it with marshes and swamps, believing that it was caused by poisonous miasmas that arose from stagnant water and were carried by damp night air. The name "malaria," meaning bad air, was first applied to the cause of the disease, and later to the disease itself.

The general nature of the disease, with the repeated asexual multiplications of the parasites in the red blood cells, and the sexual cycle in mosquitoes, is well known even to laymen, but there are some details that are not so well known, some, in fact, having only recently been discovered, yet they are of great importance. Until the last few years it was believed that the infective forms (sporozoites) injected into the blood with the salivary juice of an infected mosquito immediately entered blood corpuscles and embarked on the asexual cycle that causes the symptoms, but it has been found in some forms of bird malaria that there is a preliminary cycle in other cells, and there is reason to believe that this occurs in human malaria also.

The three common species of malaria parasites affecting man, *Plasmodium vivax*, *P. malariae*, and *P. falciparum*, are strict human parasites, unable to live in any animals but man. Other mammals, particularly bats, monkeys, and apes, have malaria parasites of their own, as do many kinds of birds and even lizards; but none of these, except one of the monkey species that is inoculable into man, affect human beings.

The general life cycles of the three human species are very similar, though they differ in details. *Vivax* and *falciparum* repeat their asexual multiplications in human blood every 48 hours, whereas *malariae* requires 72 hours. *Falciparum* differs from the others in causing the infected corpuscles to become viscid, and therefore to stick together in clusters within blood vessels in internal organs during their growth period. In this form only the young parasites that have newly attacked corpuscles, and the gametocytes, are found in the peripheral blood drawn from a finger or ear.

These differences cause differences in the clinical features. The characteristic paroxysms of chills, fever, and sweating, which many people think are the only manifestation of malaria, occur when the corpuscles burst and liberate their brood of young parasites and also various toxic products of their growth. These paroxysms occur about every 48 hours, or sometimes every 24 hours if there are two broods maturing at different times, in *vivax* and *falciparum* infections, whereas they occur every 72 hours in *malariae* infections. The 48-hour cycles are referred to as tertian malaria, the 72-hour cycles of *malariae* as quartan malaria. The tertian forms caused by *vivax* and *falciparum* are called benign and malignant tertian, respectively. The term malignant tertian is applied to *falciparum* infections because the sticking together of the viscid corpuscles clogs capillaries in various parts of the body, and in the brain may cause fatal strokes, referred to as cerebral malaria. *Falciparum* infections are, therefore, often rapidly fatal, whereas the others run long chronic courses, with relapses over periods of years, gradually lowering health and resistance to other diseases.

Although the intermittent attacks of chills and fever are characteristic of typical malaria, especially in fresh infections, this is by no means the only manifestation of malaria, contrary to popular opinion. Sometimes malaria infections cause intestinal disorders resembling cholera or dysentery, or they may cause symptoms suggestive of influenza, bronchopneumonia, lumbago, meningitis, or encephalitis. Sometimes only jaundice, anemia, kidney disturbances, or general ill health are in evidence, sometimes with no fever at all. Anyone who has lived in a malarial locality and shows symptoms of a chronic infection not otherwise diagnosed should be suspected of malaria and his blood examined for it. Failure to recognize the many forms in which chronic malaria may manifest itself has led to many a missed diagnosis.

As a case of malaria develops, immune processes increase, and the infection is kept more and more under control. *Falciparum* infections, fortunately, if untreated and the patient does not die and is not reinfected, completely die out within a year, but *vivax* and quartan infections persist, often without producing any symptoms at all, for months or years, and then relapse temporarily. It is possible that this difference may be due to the occurrence of forms of the *vivax* and quartan parasite which live in tissue cells other than red blood corpuscles, and which are unaffected by the drugs which kill the parasites in the red blood corpuscles. As we shall see later, an intensive search is being made for drugs that will kill such forms of the parasites as well as the ones in the blood that cause the acute symptoms, but so far this search has not been successful.

* * * * * * *

Let us turn now to the present status of malaria as a human scourge in the world at large. Today malaria affects every tropical and subtropical part of the world, and is one of the greatest obstacles to the colonization of these areas and to the successful economic development of industries in them. During the recent war, when large numbers of troops were operating in malaria-ridden countries in every continent on the globe, it was by far the most important medical problem with which our military organizations had to deal. Widespread as it is, however, it has lost much ground in the more northern parts of the world. A century ago it was an important disease in the northern as well as the southern parts of our own country, and even in some parts of Ontario in Canada, and in Europe it was common even in England and Holland.

The history of malaria in our own country is an interesting one. There is no evidence that it existed in the Western Hemisphere prior to colonization by Europeans. Our aboriginal inhabitants are believed to have immigrated from Asia via the Aleutian Islands during relatively warm interglacial periods, and it is easy to understand how they might have lost any malarial infections with which they started out long before they reached parts of North America where malarial mosquitoes were abundant enough to keep the disease alive and to cause fresh outbreaks.

Historical evidence shows that malaria started in the Caribbean region soon after its colonization began, and probably was the principal cause of the disappearance of the aboriginal population in the Caribbean Islands and the surrounding low coasts. When infected Negroes from Africa were brought in during the early slave days in the sixteenth century, the disease was greatly intensified. Agricultural development was so influenced by it that these Negroes, who showed superior resistance to it because of their age-old association with it in Africa, became an essential factor in the early plantations along the south Atlantic and Gulf coasts. In the seventeenth century the cultivation of rice made matters worse, and more kindling was added to the fire by the movement of infected troops during the Revolutionary War.

Following that war, malaria was carried by pioneers into the interior. These people settled along the banks of streams and rivers in the Ohio and Mississippi Valleys, where opportunities for malaria transmission were particularly good. By the early part of the nineteenth century the disease was a scourge all the way from the Great Lakes to the Gulf, and west to the prairies.

The introduction and intense development of the disease in the great central valleys was due to the interaction of many factors. First of all there was the existence of a species of mosquito, *Anopheles quadrimaculatus*, which was already at home throughout this area, which was capable of nursing the malaria parasites through their cycle of development to their infective stage, which was quite willing to feed on human blood when it was convenient to do so, and which was prone to make itself at home in and around human habitations. These mosquitoes, in spite of their ability to transmit the disease, and of habits which favored the transmission, were, of course, harmless, except for the annoyance from their bites, until they had an opportunity to acquire the malaria parasites from human carriers. This opportunity was provided by the intermingling of malaria carriers from Europe and Africa with the native white and Indian populations along the seaboards, and subsequent spread of the infections by travelers and settlers moving inland. The infection of the mosquitoes and subsequent transmission were favored by the slow travel of these early pioneers, with nightly halts near water, and by the establishment of their primitive homes along water courses where breeding places for the mosquitoes were most likely to exist. More suitable breeding places were made for them by the clearing of forest lands and admission of sunlight to swamps and edges of water courses, and by the production of new and better breeding places by the obstruction of natural drainage along roads, railways, etc., and the digging of undrained borrow pits. In addition there was, in these early days, very little livestock to divert the mosquitoes from their human victims, and in the flimsy pioneer dwellings there were no screens or other protection from mosquitoes.

With the turn of the century the pendulum began to swing the other way; a recession began, which by 1915 resulted in the complete disappearance of malaria from the area north of the Ohio River, except for temporary local outbreaks. In the Southern states the disease became geographically more restricted and less intense, although nearly 90 per cent of the South still had some malaria. Since 1915 the disease has been fluctuating with peaks and depressions about every 5 to 7 years. However, the last peak appeared in 1937 and 1938. In spite of the disrupted conditions due to the war, the rise that was due about 1942 or 1943 failed to develop, and the decline in the disease continued steadily and rapidly. In one decade, from 1934 to 1944, the average mortality rate decreased nearly 90 per cent in the 14 Southern states in which 93 per cent of the malaria deaths in the United States occur, reaching an all-time low of about 1.4 per 100,000 population. In 1944 there were only 584 malarial deaths reported from the entire United States, a rate of only 1 per 250,000 population. In the armed forces, where vast numbers of non-immune men were concentrated in camps in endemic malarious areas, the morbidity rate fell to less than 1 per cent. What a contrast to the Civil War, in which, among white Federal troops, there was an average of 2700 cases per year per 1000 men! In one Confederate force of 878 men near Savannah, there were 3313 cases in less than a year. In the middle of the nineteenth century over 25 per cent of patients in the Charity Hospital in New Orleans were suffering from fevers that were almost certainly malarial. In contrast, in the 7½ years ending June, 1940, less than 0.6 per cent of nearly half a million patients had malaria. In 1942 a typical case of malaria in Charity Hospital was sufficiently rare that the students in two medical schools were taken to see it!

In 1943 the Assistant Surgeon General of the U. S. Public Health Service outlined a plan by which he felt that malaria could be totally eliminated from continental United States within a few years, though there was a possibility that the war, and the subsequent return of thousands of infected men from overseas, might delay its successful completion.

* * * * * * *

Let us now see what had happened to bring about such a tremendous change in the space of relatively few years.

The first great step forward was the discovery of the method of transmission of the disease. Although even the ancients associated malaria with swamps and damp night air, it was not until the nineteenth century that mosquitoes began to be suspected, and not until the end of that century that their role was proved. In 1879 Sir Patrick Manson made an epoch-making discovery when he found that the causative agents of another disease, filariasis, are sucked from the blood of human victims by mosquitoes and undergo development in them, manifestly, as Manson said, on the road to a new human host. This led Manson to theorize about the transmission of malaria by mosquitoes, and to encourage an army surgeon in the Indian Medical Service, Ronald Ross, to experiment with it. After much hard labor and many disappointments, Ross's efforts were crowned with success in 1898, though he had to work with the malaria of crows instead of men; but in the same year Grassi, in Italy, proved the entire cycle for human malaria, and showed that Anopheles mosquitoes were the ones concerned.

That work placed the control of malaria on a sound scientific footing for the first time, and there were optimists who predicted that mosquito control would soon end malaria as an important human scourge. A few brilliant demonstrations of what could be done were soon forthcoming but in the world at large the optimists were disappointed, for malaria has, until now, maintained its position of pre-eminence among human diseases.

The greatest demonstrations were made by General Gorgas in Havana and Panama. Sir William Osler once stated that there was nothing to match the work of Gorgas in the history of human achievement. In 1899 the malaria rate in Havana was over 900 cases per 1000 population; in 1901 it was 151; and in 1908, 19. In 1906 Gorgas undertook disease control in the Panama Canal Zone. The French had given up the effort to build a canal after losing $200,000,000 and 50,000 lives. In 1906 the hospital admissions for malaria in the Canal Zone were 821 per 1000 population; by 1913 Gorgas had it down to 76. If it can be assumed that without the work of Gorgas the American builders of the Panama Canal would have suffered from disease as did the French, then Gorgas saved the United States nearly 40,000,000 man days of illness and 71,000 deaths in the 10 years of construction of the Canal—if, indeed, it would have been built at all.

The disappearance of malaria in the northern half of the United States and its repression in the South was not, however, due to any large extent to efforts specifically directed against the disease. A number of incidental factors contributed to it. For malaria to remain permanently endemic, three things are necessary: (1) adequate numbers of transmitting mosquitoes, (2) human beings with parasites in their blood from which the mosquitoes could become infected, and (3) opportunities for contacts between the infected mosquitoes and uninfected humans. A slight increase in any one of the three may lead to violent outbreaks, even epidemics, whereas slight decrease in any one may lead not only to a decrease but eventually to complete eradication of the disease.

It happened in the United States that in the last half of the nineteenth century and early part of the twentieth, all three factors were almost simultaneously decreased in most parts of the country. Anopheles were reduced in numbers by a vast amount of agricultural drainage, especially in some of the Northern states, and also, but to a less extent, by antilarval measures in the form of oil films, Paris green dusting, and stocking of ponds with mosquito-eating fish. Human sources of infection were reduced in number by more limited migrations, and more effective treatment. The reduction in cost of quinine from $4.50 an ounce in the 1880's to 25 cents in 1913 was a big factor in this connection. The opportunity for contacts between patients and mosquitoes, and subsequently between the mosquitoes and fresh victims, was reduced by better housing with good screening, and the use of spray guns for killing mosquitoes in houses, now almost as common household appliances as brooms.

It was the combination of these factors that caused the virtual elimination of malaria from the Northern states and its decrease in intensity in the Southern ones. It was the continuing effect of these changes, together with education of the public in proper treatment, decrease in use of ineffective chill tonics that 20 years ago were advertised everywhere on barns, outhouses, and billboards, and training of medical and public health personnel in the techniques of diagnosis, treatment, and control, that brought malaria to its unprecedented low point in the present decade, and made its eventual complete elimination a real hope.

Even now, however, civilian malaria deaths are high relative to the number of cases, in spite of the fact that with adequate diagnosis and treatment almost all of them could be prevented. In 1940 detailed information was obtained on 101 persons who were reported to have died of malaria in Georgia. Of these, 50 per cent of the whites and 75 per cent of the Negroes were ill a week before calling a physician, and 13 per cent and sixteen per cent, respectively, for a month; 38 per cent were so ill that they died within two days. This, of course, was attributable to lack of education of the public with respect to the importance of medical care in cases of fever, and persistence of faith in chill tonics and home remedies. But more disturbing was the fact that so many died in spite of early diagnosis and treatment. About 40 per cent failed to receive adequate treatment, and in only half of them was a blood smear examined at all. Moreover, the fact that only half of the positive blood examinations were diagnosed as having malignant tertian malaria, which is the only form of malaria commonly causing death directly, suggests error in diagnosis. Failure to make correct diagnosis or to make any blood examination at all, together with failure to use adequate treatment, is a reflection on medical education, and calls attention to the neglect of parasitology in medical schools.

Then came the war. Millions of troops were concentrated in camps, many of which were in the heart of endemic malarious areas, a condition that in the first world war had led to a great increase in malarial cases. Before long vast numbers of military personnel were exposed to malaria in many of the worst malarial localities in the world, including Italy, North Africa, India, Burma, and many South Pacific islands. The results were strikingly different at home and overseas. In this country the military establishments undertook malaria control within their reservations, and the U. S. Public Health

Service organized a division of Malaria Control in War Areas which undertook to control malaria within a radius of a mile, the usual maximum flight range of our malaria-carrying Anopheles, around all military establishments and defense industries, including cities where military or defense personnel lived. The result was that not only was there no increase in malaria at a time when a 5-year peak would have been expected because of unexplained natural phenomena entirely apart from troop movements, but malaria in both military and civilian personnel continued to drop to the lowest level in the history of the country.

The situation overseas was vastly different. There malaria was by far the biggest medical problem with which the medical departments of the Army and Navy had to contend. The first impact of it was felt in Bataan; it was malaria and dysentery that precipitated the fall of that bastion. In New Guinea malaria was so bad that it made it questionable whether our troops could fight successfully, although military necessity made it imperative. In the early Solomon Islands campaigns malaria caused a tremendous amount of sickness. Unprecedented exposure to infection, failure of the quinine supply, inexperience with the disease on the part of a large percentage of the medical men, and lack of personnel trained in control measures all contributed to the havoc wrought. The lack of knowledge of malaria was mainly due to its having been neglected as an important study in the majority of the medical schools of the country, especially in the North. One of my good friends who was in charge of a large hospital for returning veterans in 1943 told me that of the twenty physicians working that hospital, not one had ever seen a case of malaria before his assignment there, yet malaria was the commonest cause of disease among the patients dealt with.

In spite of this bad start at the beginning of the war, by the end of two years of fighting in the South Pacific, the struggle against malaria had been so successful that instead of being a liability, it had become one of our most valuable assets, for the cases in the opposing Japanese forces then numbered about 3½ to one of ours. Instead of making us lose battles, it contributed very greatly to victory.

What had happened? The answer can be given in two words, *education* and *research*. Our armed forces recognized the dilemma and performed a veritable miracle in correcting it. Medical men, entomologists, sanitarians, and engineers in and out of the services were educated in diagnosis, treatment, and control; and researches to develop new and better methods in all these phases of the subject were undertaken by the armed forces themselves, by various other public agencies, and by private universities and industrial laboratories. Probably no other project except the development of the atomic bomb was as intensely investigated by so many organizations and individuals.

* * * * * * *

I should like briefly to tell you of some of the developments in treatment and control. The treatment of malaria began with the use of bark from the cinchona tree, originally a native of South America. In the seventeenth century Europe was importing Peruvian bark for the extraction of balsam of Peru, which had some non-specific medical value. When this bark began to get scarce, exporters substituted another bark, later known as cinchona, which resembled it; gradually it became clear that for malarial fevers this was far superior to the other. Thus, as one writer pointed out, we owe the discovery of one of our most useful therapeutic remedies to dishonest traders rather than to keen-eyed scientists.

It was nearly two centuries later, in 1820, that quinine was extracted from the bark, and subsequently other alkaloids. Altogether there are four common ones, all with therapeutic value. During the last half of the nineteenth century large cinchona plantations were developed in several parts of the world, but most of the drug came from Java.

Until the outbreak of World War II, quinine or a mixture of the cinchona alkaloids, called totaquine, was almost universally used as a specific treatment for malaria. However, in 1924 the Germans synthesized a drug called plasmoquin, which was a valuable adjunct to quinine because it has a unique effect on the sexual forms of the malaria parasites which cause infection in mosquitoes, although it has little or no effect on the asexual forms which cause the disease symptoms. Quinine is just opposite in this respect. In 1930 the Germans synthesized another drug, atabrine, which appeared to be as effective as quinine, but it is a dye which causes temporary yellowing of the skin, and seemed to have no great advantages over quinine; so at the outbreak of the war it was still not well known to either physicians or the public.

When the Japanese cut off the supply of quinine by their operations in Asia, at a time when quinine was needed more than ever before, we of necessity turned to atabrine. Within two years it became clearly evident that atabrine was not only as good as quinine for most malarial conditions, but was actually the drug of preference except in critical cases where a large concentration of a drug is needed in the blood stream at once. Like quinine, however, it is effective only against the disease-causing asexual forms of the malaria parasites, having very little effect on the sexual forms by which mosquitoes become infected.

Not only are quinine and atabrine useful for the treatment of malaria, but both can be used, though atabrine more effectively, as a prophylactic, by taking small doses at regular intervals. Until tested on a large scale in military forces highly exposed to malaria, there was much difference of opinion about how prophylactic doses should be taken. Within a year a procedure was worked out by which cases of *falciparum* malaria, which is the most deadly, could be entirely prevented, and *vivax* malaria could be prevented from producing symptoms as long as the prophylactic doses were taken. This kind of malaria, however, is merely suppressed, and asserts its presence by production of symptoms when the preventive doses are stopped.

Both atabrine and quinine, though usually capable of either preventing or curing *falciparum* malaria, fail to cure completely a very high percentage of cases of *vivax* malaria, the result being that relapses occur at irregular intervals, sometimes for years. Moreover, as already pointed out, prophylactic doses fail to prevent infection with *vivax* or quartan malaria from developing after the treatment is stopped.

These facts were very confusing. So also was the fact that even though relapses subsequently occur, no evidence of the existence of blood infection can be found in the periods between relapses, or after adequate treatment to relieve symptoms.

The confusion was due to our having held, for years, too simple a concept of the life cycle of the malaria parasites in the human body. As I briefly mentioned earlier, it has been found in certain kinds of bird malaria that the sporozoites injected by mosquitoes do not immediately enter red blood corpuscles, but first enter fixed tissue cells, where they go through two or more multiplications. In fact, in some species these exoerythrocytic forms, as they are called, continue to exist along with the blood parasites for a long time, and in some species there is evidence that the blood forms can revert to life in fixed tissue cells.

These exoerythrocytic stages have not yet been demonstrated in human beings but it is almost certain that they exist. Thirty minutes after a person has been injected with sporozoites taken from mosquitoes, these sporozoites disappear from the blood stream, and continue to hide out until 7 to 9 days later. In some kinds of malaria not all the tissue parasites are expelled into the blood stream at once; some may persist in the tissue cells for a long time. It is also possible that blood forms may later revert to the tissue cells. On this theory, malarial relapses would be due to the periodic expulsion of parasites into the blood stream followed by multiplication in it. If there is a short period of development in fixed tissue cells followed by expulsion of all of them into the blood stream, we would have a disease that runs a short course, is not subject to relapses at distant dates, and could be prevented or cured by drugs such as quinine and atabrine which kill the parasites that are in the blood stream. Such is the disease caused by *falciparum* malaria. On the other hand, if there is persistent development of some of the parasites in the fixed tissue cells, or reversion to this by some of the blood parasites, we would have a disease that runs a long-drawn-out course, with irregular relapses, and not preventable or curable by quinine or atabrine, which kills the blood forms but not the tissue forms. Such is the disease caused by *vivax* and quartan malaria.

On this concept it can readily be seen why attempts of physicians to cure *vivax* or quartan infections by means of quinine or atabrine were doomed to failure, in spite of trial of every conceivable and possible method of administering the drugs. What was needed was a drug that would kill the tissue forms of the parasite.

Intensive research during the war years was carried out to find a drug that would be a true causal prophylactic rather than a suppressive, and also cause complete cures, with no danger of relapse. If such a drug could be found it would be a major achievement, and go far towards the ultimate eradication of the disease. Many thousands of compounds have been tested in dozens of laboratories. The general procedure is to test them first on birds. Birds are fed the experimental drugs in their food, either before or after infection with sporozoites of various species of bird malaria, to test both prophylactic and curative effects. If the drugs show no activity they are discarded, and those showing promise are tested on human beings. Although no drug has yet been found which has so far been proved to have the properties desired, it is interesting and encouraging that some antimalarial action has been found in about 5 per cent of the drugs tested, and some of the drugs found are believed to be superior to atabrine. Some laboratories were able to test over 200 drugs per month. It may confidently be expected that this intensive research will result in discovery of the desired drug before long. In the meantime at least two drugs, chloroquine, developed by the National Research Council, and paludrine, developed by the British, have been discovered that appear to be superior to atabrine, and will probably come into wide use when commercially available.

In the field of control two great strides have been made since the outbreak of the war—the development of aerosols, and the application of DDT to Anopheles control.

Prior to the war, as I have already mentioned, sprays were extensively used to kill adult mosquitoes in houses, barracks, native huts, etc., either as an adjunct to control of mosquito breeding, or as a substitute for it. In some places in India and Africa malaria was reduced by as much as 90 per cent by the simple expedient of spraying human habitations with insecticides once or twice a week, at a ridiculously low cost. In some places in India the cost was estimated at only 8 cents per year per person. By this method were killed a high percentage of the house-frequenting species of Anopheles which had recently bitten human beings and would eventually become transmitters if permitted to live, or which, after becoming infective, had entered houses to feed on fresh victims. The most effective spray was an extract of pyrethrum dissolved in kerosene or other oil solvent. Pyrethrum is extracted from the heads of a species of chrysanthemum that originally grew in Dalmatia, like a yellow daisy, but has since been extensively cultivated in other parts of the world. The toxic substances penetrate the cuticle of insects and affect the central nervous system, with a narcotizing effect. They are, however, non-toxic to man and domestic animals. A spray that is deadly to mosquitoes can be prepared for only about 15 cents a gallon.

Early in the war it was found that if the pyrethrum was dissolved in a volatile substance like freon, liquefied under pressure, it was far more effective. When liberated from a container as a fine mist the freon evaporates and leaves the active insecticide in almost molecular form in the air where, if in a closed room, it stays in suspension, and penetrates into every crevice and corner. Small "bombs" were manufactured which contained enough insecticide to kill mosquitoes in 150,000 cubic feet of space. Opening such a bomb for a few seconds in an ordinary-sized room or tent was all that was necessary to destroy the mosquitoes in it. These mosquito bombs played a large part in the control of malaria in the early years of the war.

Then came the discovery of the effectiveness of DDT against both the larvae and adults of Anopheles mosquitoes.

This was one of the major scientific achievements of the war. Prior to DDT the principal methods for control of Anopheles larvae in swamps, marshes, edges of ponds and streams, rice fields, etc., was either the spraying of oil films or dusting with Paris green diluted with some inert dust. DDT proved to be more effective in smaller amounts. Its effectiveness is well illustrated by an incident that occurred in early experiments on its effectiveness. Two ponds which were active mosquito breeders were selected for a test, one being treated, the other kept untreated as a control. The treated pond promptly ceased to breed mosquitoes but strangely enough the control pond did too. It was eventually discovered that ducks flying from the treated to the untreated pond carried enough DDT on their feathers to prevent mosquito breeding in the control pond.

The effectiveness of DDT against different kinds of insects varies greatly. Houseflies, for instance, are killed by a concentration so low that if one ounce could be uniformly distributed over 110 square miles of surface, they would be killed by resting on this surface. Against mosquitoes, possibly because of their smaller feet, the effect is not quite so spectacular, but is nevertheless remarkable.

When DDT is sprayed from airplanes, either dissolved in non-volatile solvents or as a dust, it is possible to get 90 per cent to 100 per cent control by the use of as little as one to two quarts per acre of an emulsion or solution containing about half an ounce of the chemical. The use of such methods in the South Pacific is what made our campaigns there possible. I have been told that the DDT treatment of some islands was so effective that almost all insect life was destroyed so completely that it was not even possible to grow such things as tomatoes, because of absence of insects to pollinate the flowers. In a test treatment made in a jungle-bordered area in Panama, 15,000 mosquitoes were caught in a horse trap and later released, and an average of a dozen larvae of the local malaria-carrying Anopheles were caught in each of 200 dippers of water the night before the treatment. Twenty-four hours after spraying the area with DDT, only 86 mosquitoes were caught in the horse trap, and not a single larva was dipped up.

Even more striking is the effect of this remarkable chemical on adult mosquitoes. The DDT, if applied as an aqueous emulsion on walls or other surfaces where the insects rest, not only kills them at the time of application, but has a residual effect which lasts for months. In other words, after the walls of a room have been sprayed, mosquitoes entering any time thereafter for two or three months will die after resting on such a wall for a few minutes. The chemical, which has no repellent effect on the insects and is therefore more dangerous for them, is slowly absorbed through the feet, and by an effect on the nervous system which is not yet fully understood, causes twitching, then paralysis, and finally death. The mosquitoes begin to fall in from 8 to 10 minutes, and the majority are down within an hour. Many become restless and leave the room or house before they die, but not before they have absorbed a fatal dose. Since Anopheles mosquitoes usually rest on surfaces for considerable periods of time before and after feeding, it is obvious that the majority of those biting malarial patients in or around houses that have been sprayed will be killed before they can transmit the disease.

During the war, DDT was not available in sufficient quantity for civilian use, all of it being required for protection of military personnel. In 1945, however, due to a tremendous increase in production and to a reduction in the amount required for military purposes, it became available for civilian use. The U. S. Public Health Service then, to meet the impact of returning servicemen who had contracted malaria overseas and were returning to civilian life where they might be a means of increasing malaria at home, inaugurated what was called an Extended Malaria Program. With the coöperation of State Health Departments, malaria control crews went into selected counties where malaria was still relatively common, and undertook to spray with DDT every house and privy in rural areas and in towns of less than 2500 population.

Contact men preceded the spraying crews to acquaint the residents with what was to be done and to get them to prepare their homes for spraying. With power sprays they then covered every wall and ceiling, the backs of large pieces of furniture, and the screens and porches, with a 5 per cent emulsion of DDT. The result was not only destruction of the majority of Anopheles mosquitoes that entered the houses and privies, but also a riddance of other mosquitoes, flies, gnats, fleas, roaches, and other insects, leaving the homes practically insect free for periods of many weeks. It is not 100 per cent effective, of course, partly because occasionally the spraying is not adequately done, partly because some transmission of malaria takes place outside of houses or privies, and partly because Anopheles like to rest on spider webs, and sometimes succeed in resting on freshly spun threads, unharmed, a fraction of an inch away from the deadly walls. The recommended dosage is about 4 cc.—1 teaspoonful—of 5 per cent DDT per square foot of wall surface, although a fourth of that is sufficient under favorable conditions. After the xylene and water of the emulsion have evaporated, usually within a half hour, the DDT is left as a practically invisible film of microscopic crystals on the walls. These crystals do not volatilize, but gradually flake off, or are rubbed off, and appear to be affected by continued exposure to sunlight; so the period of effectiveness may vary from two or three months to six months. In this crystalline form DDT is harmless—a child would have to lick off about 10 square feet of surface to get a harmful dose. The cost, including labor, has been estimated at an average of about from $1.00 to $1.50 per house.

It is too early yet to evaluate the results of this residual spray procedure, but the preliminary reports on reduction of malaria in treated counties are encouraging. There is every reason to believe that this method of control will so reduce the number of infective bites by malaria-infected Anopheles, that the mathematical chances will be against the successful continued transmission of the disease. As human cases become fewer, and carriers gradually lose their infections by natural development of immunity or repeated treatment to suppress the blood forms of the parasites, it may confidently be expected that the disease will gradually die out in the South as it did a few decades ago in the North.

Only the counties having an appreciable amount of malaria need be treated. In the others, if contact with cases acquired in the more severely affected areas is cut off, the disease will probably disappear without this added procedure, merely as the result of better drainage, better housing, and more adequate treatment, as it did in the North, in spite of a fairly large population of Anopheles mosquitoes. If in addition the intensive search for a drug that will eliminate the relapsing tertian form of the disease is successful in the near future, we may confidently look forward to the complete extermination of endemic malaria in this country, although occasional local outbreaks from cases imported from abroad will be likely to occur. When they do, they should very quickly and easily be snuffed out.

For a time it was feared that one result of the war might bleach the rosiness of this picture. That was the possibility that some of the exotic strains of malaria from distant parts of the world, particularly the South Pacific, when introduced into this country by returning servicemen, might be sufficiently different and more dangerous than our local strains that they would cause severe epidemics. Such epidemics might result from lack of immunity to these strains by people living in malarious areas where there was considerable immunity to indigenous strains; to greater susceptibility of our local mosquitoes to infection with these strains, since such differences in susceptibility were known to exist; or to less amenability to treatment, resulting in more relapses and more prolonged infectiousness of the blood of these men for mosquitoes.

Fear of the latter was heightened by experience with the disease in some of the first veterans who were hospitalized with it after their return to this country. These men seemed to be abnormally prone to relapse, and resistant to treatment. This, however, proved to be an illusion, for there had already been a selection of the cases more prone to relapse. The patients who continued to relapse after several courses of treatment were the ones who were invalided home, thus increasing the percentage of chronic relapsers over what would normally be expected. Research has also demonstrated that immunity to local strains of malaria extends to the imported South Pacific strains, and that our local mosquitoes are not more susceptible to the imported strains than they are to the home varieties. There is no longer reason to fear that these exotic strains are in any way more harmful than those already existing here.

The war, then, has not dimmed the outlook for the elimination of malaria in this country in those ways about which there was considerable apprehension. On the other hand, it has actually brightened the picture, for at no time in history has malaria received the widespread recognition and publicity to which it has been subjected in the past two or three years. Its military significance, the high initial casualty rate among overseas troops, and the widely publicized though fortunately unfounded fear of the effect of returning malaria carriers have led to unprecedented public awareness of the disease, a better understanding of the harms it can do, and more interest in its control.

The outlook for the conquest of malaria in many places in the tropics is not so immediately hopeful. The fight will be longer and more difficult, but I believe it possible that within a generation the results of improved methods of treatment and control, largely growing out of research carried on during the war, will eventually bring malaria under sufficiently good control that, instead of being Public Enemy No. 1 among human diseases, it will be relegated to a comparatively unimportant status. The saving in human life and suffering and in economic status in malaria-ridden countries will be incalculably great.

In the past, malaria control has been greatly hampered by lack of education, and by social obstacles to the effective use of control methods that were available. There has been limited use of sound administrative principles in public health work due to lack of sufficiently trained personnel for organizing and carrying out the work; ineptness in the application of control methods; and lack of interest on the part of the general population because of failure to realize the terrific cost of malaria on health, happiness, and economic status and to appreciate the benefits to be derived from adequate control. There has also been widespread ignorance or inattention to conditions that lead to malarial outbreaks; a high percentage of malaria is man-made, resulting from breeding places near villages or industries or public works created by irrigation projects, borrow pits, impeded drainage, etc., largely due to ignorance or carelessness on the part of civil engineers. During the war, bomb craters, foxholes, and shell holes made many a malaria mosquito happy, for under natural conditions even mosquitoes are affected by what corresponds to a housing shortage. Man is an occasionally rational being who, until recent years, has probably done as much to help malaria as he has done to eradicate it.

In many places the failure to determine the particular species of mosquitoes that were mainly responsible for the transmission of the disease, and to study the habits, especially the breeding habits, of these mosquitoes, has resulted in large expenditures for work that has been ineffective. The methods used in controlling malaria mosquitoes in one place may be totally ineffective or even lead to *more* malaria in another place. Anyone who attempts to fight malaria without first finding out what mosquitoes are the principal carriers of it, and learning where and how they breed, would be as handicapped as a fisherman who tried to use the same methods for catching rainbow trout, herrings, catfish, and eels, or a hunter who went after bobwhite, ducks, squirrels, and rabbits in the same places and with the same equipment.

Many a time in the past, lack of entomological research has led to extensive efforts to control mosquitoes that play no appreciable role in the transmission of malaria, or to apply methods that were entirely ineffective. A good example was afforded in Trinidad, where extensive drainage and ordinary antilarval measures caused no appreciable diminution in malaria, because the principal species concerned there bred in water held by aerial plants growing in trees used to shade cacao groves. In Malaya, malaria is carried in the lowlands by a species of Anopheles that breeds only in shade in standing water; in the hills it is carried by a species that breeds only in running streams exposed to sunlight. Removing shade in one place would greatly reduce malaria, in the other increase it.

Species control directed against the particular species of mosquitoes that have been proved to be important has supplanted the old method of indiscriminate control. Nowhere have the effects of this been more strikingly demonstrated than in Brazil. There an imported African mosquito, *Anopheles gambiae*, caused a terrific epidemic in 1938, with 100,000 cases and 14,000 deaths in the first six months of that year, in some areas affecting over 90 per cent of the population. As one writer expressed it, human language is inadequate to describe the desolation which existed in the region, in which suffering, tears, and mourning spread their lugubrious mantle over thousands of graves. It was generally believed that the Northeast of Brazil would be depopulated because those who did not die at once would abandon it. This was bad enough, but there was sound reason for believing that continued extension of the mosquito, with its disease-carrying propensities, was a threat to every country in the Western Hemisphere except Canada. To make a long story short, a careful study of the habits of this one mosquito, and a concerted effort by the Brazilian government and the Rockefeller Foundation, resulted in the complete extermination of this species in the Western Hemisphere within a little over two years. Incidentally, living specimens, undoubtedly newly imported, have been caught twice since this extermination in or near the airport at Natal, Brazil, showing the extreme importance of disinsectization of aircraft in this age of aerial transportation. During the war this same species was introduced into Egypt from Sudan, with results comparable to those in Brazil.

To sum up, then, the outlook for the conquest of malaria in the United States looks bright for the very near future.

In the tropics it looks brighter than it ever has before, though attainment will be slower and more difficult. Enlightened public opinion, awareness of the importance of malaria by governmental and industrial agencies, the training of adequate personnel for the application of control measures, improved methods of treatment, research on the species of mosquitoes locally involved in transmission, intelligent concentration of effort against these particular mosquitoes, and the use of newly discovered and more effective control methods—all these things will contribute to the ultimate downfall of the disease that has, until now, caused more human suffering and degradation than any other.

ASA C. CHANDLER.